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CASE REPORTS

Implication of AV node blockers in patients with end-stage renal disease undergoing head and neck surgery; BRASH syndrome: a case report

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Abstract BRASH (Bradycardia, Renal failure, Atrioventricular [AV]-node blocker medications, Shock, and Hyperkalemia), a novel syndrome, is a synergistic interaction between AV node blockers and hyperkalemia, resulting in bradycardia. We report a case of BRASH syndrome with marked bradycardia in a patient with End-Stage Renal Disease (ESRD) associated with synergistic interaction between mild hyperkalemia and AV node blockers. Anesthesiologists should be aware of these clinical features, in which ESRD patients with baseline mild hyperkalemia are particularly susceptible to bradycardia. This report will help in its early recognition as well as enable comprehensive and appropriate treatment strategies without further invasive therapy.

Introduction

Severe hyperkalemia manifests as reversible bradycardia mimicking Atrioventricular (AV) blocks of variable severity.[1] However, under AV node blocker medication, hyperkalemia can cause hemodynamic instability and refractory bradycardia even in the absence of severely elevated potassium levels or significant intake of AV node blockers. BRASH (bradycardia, renal failure, AV node blockers, shock, and hyperkalemia) syndrome is a synergistic phenomenon involving hyperkalemia, AV node blockers, and renal failure and can cause cardiovascular collapse.[2] Most experienced anesthesiologists have successfully managed patients with BRASH syndrome without recognizing its specific pathophysiology. Nevertheless, defining this syndrome and recognizing its mechanism might optimize patient diagnosis and management. Therefore, we report BRASH syndrome with marked bradycardia in a patient with End-Stage Renal Disease (ESRD) associated with synergistic interaction between mild hyperkalemia, and AV node blockers.

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Table 1 Arterial blood gas analysis.

	Preoperative	Induction	Event	1h after event
pH	7.45	7.47	7.38	7.31
PaO_2 (mmHg)	100	179	218	136
PCO_2 (mmHg)	40.7	38	46	41
HCO_3- ($mM.L^{-1}$)	28.0	27.7	27.2	26.4
Na ($mmoL.L^{-1}$)	136	133	127	132
K ($mmoL.L^{-1}$)	4.2	4.5	5.8	4.2
Ca++ ($mmoL.L^{-1}$)	1.05	1.02	1.01	1.09
Glucose ($mg.dL^{-1}$)	143	154	178	161
Lactate ($mmoL.L^{-1}$)	1.18	1.1	2	2.9

Case report

A 71-year-old man (height 170 cm, weight 59 kg) was scheduled to undergo wide excision with marginal mandibulectomy and Pectoralis Major Myocutaneous (PMMC) local flap surgery for oral cavity cancer treatment. His medical history included type 2 diabetes mellitus, hypertension, and ESRD. The patient underwent hemodialysis three times a week, and his medications included amlodipine, nifedipine, valsartan, carvedilol, and insulin. Preoperative laboratory findings revealed chronic kidney disease (Stage 5) with increased blood urea nitrogen ($28.9\ mg.dL^{-1}$) and creatinine ($6.23\ mg.dL^{-1}$). Creatinine clearance was 7.61 mL/min based on the Cockcroft-Gault equation. However, other electrolytes and thyroid hormone levels (thyroid stimulating hormone 3.08 U/mL and free T4 $1.29\ ng.dL^{-1}$) were within the normal range (Table 1). Preoperative Electrocardiography (ECG) and transthoracic echocardiography revealed no abnormal findings except for left ventricular hypertrophy and diastolic dysfunction (Grade 1). Patient was transferred to the operating room without premedication. Standard monitoring was performed during surgery, including ECG, noninvasive blood pressure (NIBP), end-tidal CO_2 concentration, and pulse oximetry. His initial vital signs were NIBP, 139/56 mmHg; SpO_2, 100%; and heart rate (HR), 63 beats/min. Anesthesia was intravenously (IV) administered using 80 mg 2% lidocaine, 120 mg propofol, 50 mg rocuronium, and 50 μg fentanyl. The patient was successfully intubated, and anesthesia was maintained using desflurane 5–7 vol% in 50% oxygen and remifentanil $0.05–0.15\ \mu g.kg^{-1}.min^{-1}$. Approximately 3 hours after the beginning of the procedure, his vital signs suddenly dropped to NIBP, 81/40 mmHg; SpO_2, 100%; and HR, 31 $beats.min^{-1}$. At that time, the patient had already been performed neck dissection and marginal mandibulectomy. During the harvesting of the PMMC flap, marked bradycardia and hypotension were noted. Therefore, the carotid sinus reflex and excess vagal tone caused by vagus nerve traction, which is occasionally observed during head and neck surgery, can be excluded. ECG continued to reveal marked bradycardia (HR 31–36 $beats.min^{-1}$) with a junctional rhythm (Fig. 1). Atropine (0.5 mg) was administered twice; however, there was no response. To treat the marked refractory bradycardia and provide inotropic support, we infused $0.1\ \mu g.kg^{-1}.min^{-1}$ isoproterenol. Arterial blood gas analysis revealed increased serum potassium levels from a baseline value of 4.2 to 5.8 $mmoL.L^{-1}$. The remaining arterial blood gas analysis parameters were normal (Table 1). Patient received IV calcium, regular insulin (10 units IV), and 50 mL of 50% dextrose. After 1 hour, potassium levels normalized to 4.2 $mmoL.L^{-1}$, and no further junctional bradycardia was observed. Considering the pentad of the hemodynamic state (bradycardia), underlying disease (ESRD), history of medication (beta-blocker), hyperkalemia, and hypotension, we diagnosed the patient with BRASH syndrome. Thereafter, we frequently evaluated his potassium levels and volume status to ensure normal levels. Surgery was successfully completed, and the patient was transferred to the surgical intensive care unit after extubation. Patient was initially scheduled for temporary pacemaker insertion; however, after hyperkalemia improvement, his HR remained normal without isoproterenol or other support. Additionally, postoperative cardiac enzymes (CK-MB $1.40\ ng.mL^{-1}$ and troponin T $0.075\ ng.mL^{-1}$) were within the normal limits. One day after surgery, the patient was transferred to the general ward without any complications.

Discussion

BRASH syndrome, which has been recently described as a pentad of the hemodynamic state (bradycardia), underlying disease (renal failure), history of medication (AV node blockers), hyperkalemia, and shock is a novel clinical entity.[2] In fact, it is well established that hyperkalemia and AV node blockers cause bradycardia.[3] However, this new entity remains under-recognized. To the best of our knowledge, this is the first case suggesting that two factors, mild hyperkalemia, and AV node blockers, can synergistically cause more dramatic bradycardia than expected with either of the two factors in patients with ESRD undergoing head and neck surgery.

The occurrence of intraoperative bradycardia may be explained by the presence of multiple factors, including hypothermia, hypothyroidism, inferior myocardial infarction, excessive vagal tone, carotid-sinus reflex, autonomic neuropathy, medication-induced, electrolyte imbalance, etc. In our case, hypothermia, hypothyroidism, and inferior myocardial infarction were ruled out by physical examination and laboratory testing. Perioperative ECG and normal troponin levels ruled out an acute ischemic event. Since the carotid sheath was not manipulated during the surgical procedure, the surgery-related causes of carotid sinus reflex or excessive vagal tone could also be excluded. Moreover, we considered the possibility of dysautonomia. In general, patients with diabetic autonomic neuropathy exhibit altered hemodynamic responses to general anesthesia, such as abrupt decreases in blood pressure and HR on induction. However, in this patient, hemodynamic instability did not occur during anesthetic induction. The intraoperative course until the development of this episode was uneventful. In addition, the patient had no history of recent orthostatic hypotension, gastroparesis, or intermittent diarrhea. Considering this, we could not find a satisfactory mechanism for dysautonomia-mediated bradycardia. Further laboratory tests showed hyperkalemia. Based on the above findings, all other possible causes that could have triggered intraoperative bradycardia were excluded, and we postulated that hyperkalemia is causally related to the

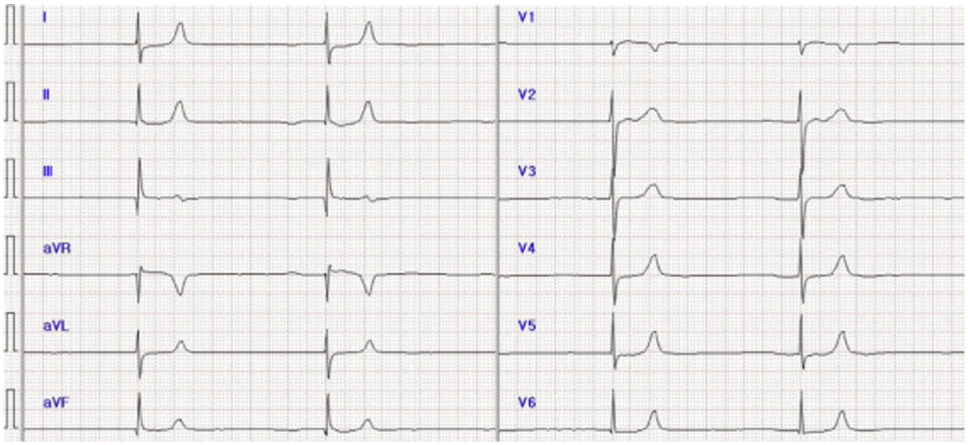

Figure 1 Intraoperative electrocardiogram demonstrating severe bradycardia (31 beats.min^{-1}) with junctional rhythm.

development of bradycardia. In general, hyperkalemia alone is not responsible for bradycardia; however, the synergy of mild hyperkalemia with accumulated AV node blockers in patients with ESRD may result in the clinical picture noted here.

BRASH syndrome is essentially a synergistic process triggered by a combination of hyperkalemia and AV node blockers. This report highlights the caveat that AV node blockers can lead to marked bradycardia if exacerbated even by mild hyperkalemia. As a result, cardiac output is significantly decreased, leading to shock with further worsening of renal perfusion. In turn, this can aggravate hyperkalemia, which would further increase the effect of AV node blockers and thus lead to a vicious cycle of BRASH syndrome. A previous report demonstrated that only severe hyperkalemia (e.g., potassium level > 7 mEq.L^{-1}) causes bradycardia.[4] This may differentiate it from BRASH syndrome, in which patients only have mild to moderate hyperkalemia. Another important differentiating feature is the presence of AV node blockers, which is a feature of BRASH syndrome. In addition, the patient's ECG demonstrating severe bradycardia without other electrocardiographic features of hyperkalemia is another main indication of BRASH syndrome. In general, preoperative intoxication of AV node blockers may also cause bradycardia and shock. The most important factor distinguishing it from BRASH syndrome is the patient's clinical history. BRASH syndrome does not include supratherapeutic medication levels but is rather caused by a synergy between mild hyperkalemia and therapeutic medication levels of AV node blockers. In our case, the patient was compliant with his medication use and denied the overuse of AV node blockers. Therefore, BRASH syndrome is located in the center of a continuum from severe hyperkalemia to an overdose of AV node blockers. Although it is not always possible to accurately determine the location of these boundaries, attempting to make any distinction among these disease states is useful for patient management.

Unfortunately, the most common flaw in managing patients with BRASH syndrome is only focusing on a single component (e.g., hyperkalemia), resulting in the overlooking of other features of this syndrome (e.g., renal failure, AV node blockers, and bradycardia). Therefore, understanding its pathophysiology is important to enable a coordinated treatment strategy covering all its components. BRASH syndrome management involves hemodynamic support, prompt hyperkalemia correction, and bradycardia treatment. First, hyperkalemia should be promptly treated, even if relatively mild. Treatment should be initiated with IV administration of insulin, glucose, and calcium for membrane stabilization, which is also the standard treatment for severe hyperkalemia. The Advanced Cardiac Life Support (ACLS) bradycardia algorithm does not use IV calcium and therefore does not appropriately treat BRASH syndrome.[5] Hence, blindly following the ACLS bradycardia algorithm without an accurate awareness of BRASH syndrome may lead to the overuse of transvenous pacing. In other words, this algorithm can result in unnecessary placement of transvenous pacemakers in patients who could have responded to medical treatment. This is another reason for the clinical importance of understanding and recognizing BRASH syndrome. In our case, bradycardia was also treated with a combination of beta-agonists (isoproterenol) and IV calcium. In fact, when the patient did not respond to atropine during surgery, we planned emergency hemodialysis and temporary pacing. However, after hyperkalemia was corrected, his condition stabilized, and no further management was required.

BRASH syndrome is a clinically under-recognized diagnosis, and its presentation is quite variable. In marked bradycardia and shock, which occur suddenly during surgery, rapid and adequate treatment can be difficult without the accurate knowledge of BRASH syndrome. Therefore, the availability of a relatively recently established concept of BRASH syndrome may enable early diagnosis and treatment and may help improve patient prognosis.

Conclusions

Patients being treated with AV node blockers and undergoing hemodialysis for ESRD are susceptible to BRASH syndrome even in the presence of mild hyperkalemia intraoperatively. Therefore, anesthesiologists should be particularly vigilant about the anesthetic management of these patients by closely monitoring serum potassium levels and ECG during

the perioperative period. Understanding BRASH syndrome may help in its early recognition, enabling comprehensive and appropriate treatment strategies without further invasive workup.

Informed consent

This case study was approved by the institutional review board of our institution (IRB 2020-06-025). The need for written informed consent was waived due to the nature of the study.

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Conflicts of interest

The authors declare no conflicts of interest.

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